[11] Patent Number:

4,529,719

[45] Date of Patent:

Jul. 16, 1985

[54] MODIFIED CROSSLINKED STROMA-FREE TETRAMERIC HEMOGLOBIN

[76] Inventor: 1

Ross W. Tye, 937 B Rosenstock Rd.,

Sausalito, Calif. 94965

[21] Appl. No.: 497,454

[22] Filed: May 4, 1983

[51] Int. Cl.³ A61K 37/00; A61K 35/14; A23J 1/06; C07G 7/00

[58] Field of Search 260/112 B, 112 R, 112 S; 424/177, 95, 101; 546/298; 560/143

[56]

References Cited

PUBLICATIONS

Tye, Ross W., *Prog. Clin. Biol. Res.* Apr. 1983, vol. 122, pp. 41–49 "Modification of Hemoglobin-Tetrameric Stabilization".

Walder et al., *Biochemistry*, vol. 18, No. 20, 1979, pp. 4265-4270, "Diaspirins that Crosslink β Chains & Hemoglobin . . ."

Greenburg et al., Surgery vol. 36 (1) pp. 13-16 1979, "Intravascular Persistence and Oxygen Delivery . . . ". Walder, Joseph et al., J. Mol. Biol. vol. 141, pp. 195-216

1980, "Development of Antisickling Compounds . . . Binding Site".

Primary Examiner—Blondel Hazel Assistant Examiner—Robin Teskin

Attorney, Agent, or Firm-Townsend and Townsend

[57]

ABSTRACT

Stroma-free deoxy mammalian tetrameric hemoglobin is crosslinked with certain bis diaspirin esters and modified with pyridoxyl-5'-phosphate followed by reduction to produce bis-diamide covalently crosslinked, pyridoxal-5'-phosphate covalently modified tetrameric hemoglobin wherein the crosslinking and modifying bonds occur in the beta cleft. The modified crosslinked stroma-free tetrameric hemoglobin of this invention is a disease-free, oxygen transporting discrete molecular species, free from cell surface antigens, having use as a substitute for transfusion of red blood cells. This modified crosslinked stroma-free hemoglobin is a stable oxygen carrying protein capable of oxygen delivery to perfused tissue and advantageously remaining in the intravascular space.

23 Claims, 3 Drawing Figures